A 75-year-old man comes to the urgent care center with acute onset of a pruritic rash after eating strawberries. The patient has no associated swelling in or around the mouth, no wheezing, and no difficulty breathing. Past medical history is notable for coronary artery disease, for which he takes atorvastatin, lisinopril, aspirin, and metoprolol. He also has a history of allergy to dog and cat dander. The patient does not use alcohol or tobacco. His family reports that he lives alone and his functional status has been declining. He walks with a cane, has poor vision, and is frequently forgetful. The patient also has occasional dizziness when standing up and a history of frequent falls. Which of the following would be the most appropriate medication to treat this patient's acute symptoms?

A. Chlorpheniramine
B. Diphenhydramine
C. Hydroxyzine
D. Loratadine
E. Promethazine

Submit

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- A. Chlorpheniramine (6%)
- B. Diphenhydramine (15%)
- C. Hydroxyzine (5%)
- ✓ D. Loratadine (66%)
- E. Promethazine (5%)

Omitted
Correct answer
D

66%
Answered correctly

04 secs
Time Spent

07/07/2020
Last Updated

Explanation

This patient, with an acute, pruritic rash and history of environmental allergies, has a typical presentation of urticaria (hives). Hives are triggered in most cases by IgE-dependent mast cell degranulation. As histamine is one of the primary mediators in this type of allergic reaction, **antihistamines** (ie, H1 histamine receptor antagonists) are the preferred treatment in most cases.

The side effects of antihistamines are largely due to blockade of other pathways, especially:

This patient, with an acute, pruritic rash and history of environmental allergies, has a typical presentation of urticaria (hives). Hives are triggered in most cases by IgE-dependent mast cell degranulation. As histamine is one of the primary mediators in this type of allergic reaction, **antihistamines** (ie, H1 histamine receptor antagonists) are the preferred treatment in most cases.

The side effects of antihistamines are largely due to blockade of other pathways, especially:

- **Cholinergic/muscarinic** (blurry vision, exacerbation of glaucoma, urine retention, delirium, constipation)
- **Alpha-adrenergic** (postural dizziness, falls)
- **Serotonergic** (appetite stimulation, weight gain)

These side effects are especially prominent with first-generation antihistamines (eg, hydroxyzine, promethazine, chlorpheniramine, diphenhydramine) **(Choices A, B, C and E)**. Furthermore, first-generation antihistamines are lipophilic and easily cross the blood-brain barrier, where they may cause significant sedation and cognitive dysfunction. First-generation antihistamines are considered potentially inappropriate medications for **elderly patients**, especially those with pre-existing cognitive or functional impairment.

Newer-generation antihistamines (eg, loratadine, cetirizine) do not have the same degree of antimuscarinic, antiserotonergic, or anti-alpha adrenergic properties and their side effects are minimal. Moreover, second-generation antihistamines are less lipophilic, do not readily cross the blood-brain barrier, and are usually nonsedating.

Educational objective:
First-generation antihistamines can cause significant side effects due to blockade of cholinergic, alpha-adrenergic, and serotonergic pathways. They should be avoided in older patients with cognitive or functional impairments.

References

- Drugs with anticholinergic properties: a current perspective on use and safety.

Pharmacology	Allergy & Immunology	Antihistamines
Subject	System	Topic

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A 29-year-old woman comes to the office with a 2-month history of right lower quadrant pain and intermittent diarrhea. Vital signs are normal. The examination is unremarkable except for right lower quadrant tenderness. After confirmatory testing, the patient is given a delayed ileal-release medication that works by binding to a cytosolic receptor, translocating to the nucleus, and inhibiting nuclear factor-kappa-B (NF-κB). The patient is most likely being treated with which of the following medications?

A. Azathioprine

B. Budesonide

C. Infliximab

D. Methotrexate

E. Mycophenolate

Submit

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- A. Azathioprine (4%)
- ✓ B. Budesonide (67%)
- C. Infliximab (17%)
- D. Methotrexate (1%)
- E. Mycophenolate (8%)

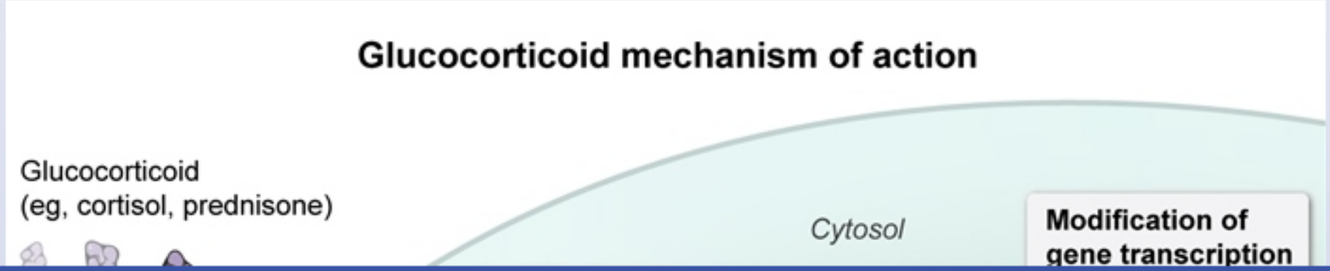
Omitted
Correct answer
B

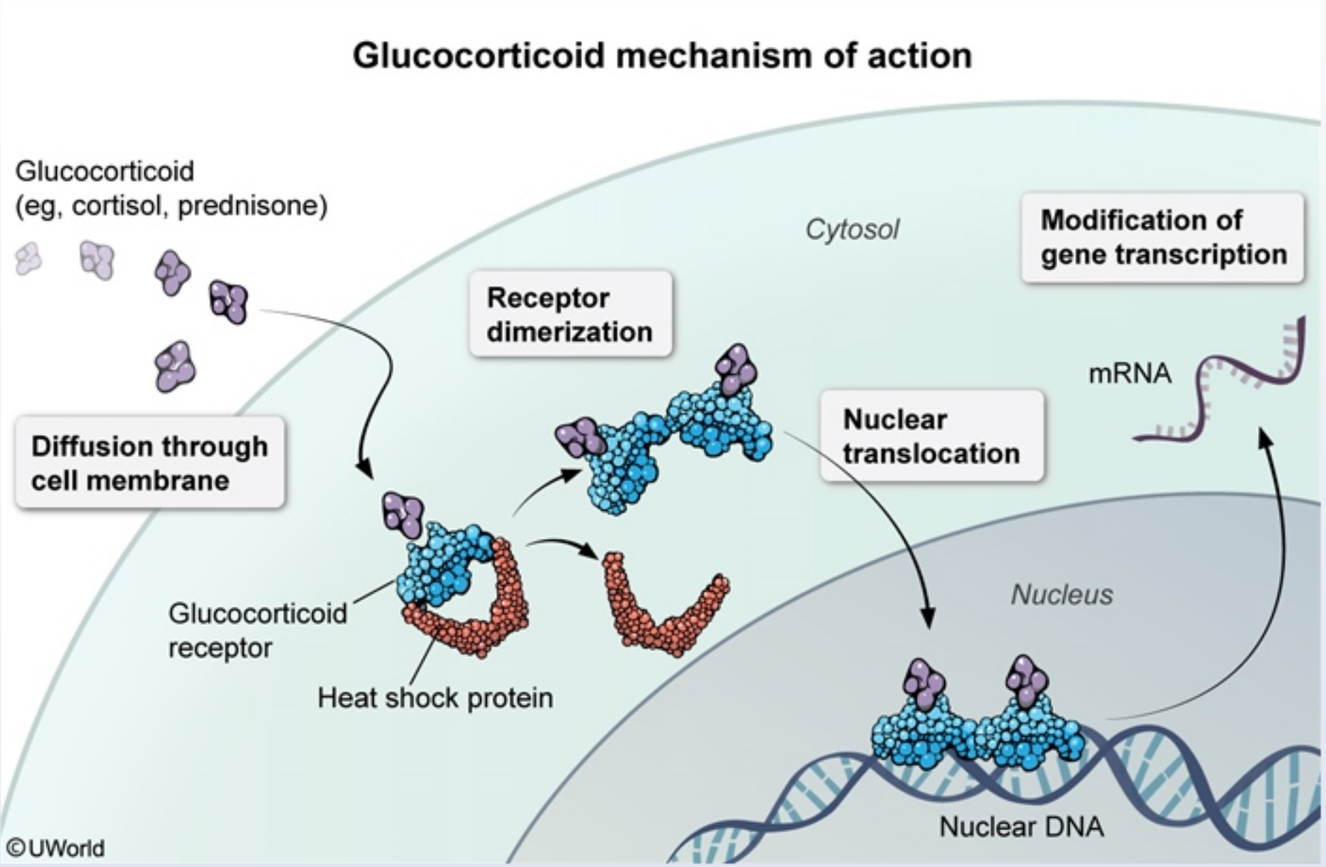
67%
Answered correctly

01 sec
Time Spent

04/20/2020
Last Updated

Explanation





This patient has chronic right lower abdominal pain with tenderness and intermittent diarrhea, symptoms that raise suspicion for **Crohn disease** with ongoing active inflammation. Patients with mild Crohn disease (eg, limited area of inflammation, no evidence of systemic involvement) are often treated with a targeted-release glucocorticoid such as budesonide to reduce inflammation and induce disease remission.

Glucocorticoids, like many other lipid-derived hormones (eg, progesterone, estrogen), bind to a **cytosolic receptor** rather than a cell surface receptor. The glucocorticoid-receptor complex can then **translocate** into the nucleus, bind to the relevant DNA regions, and cause a tissue-specific alteration in transcription. In immune cells, the effects of glucocorticoids include **inhibition** of proinflammatory transcription factors such

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Oral **budesonide** (often given in a delayed-release preparation that targets the ileum) is especially useful in Crohn disease because it has high topical potency and **less systemic adverse effects** than other glucocorticoids (eg, prednisone) due to **high first-pass metabolism**.

(Choices A and E) Azathioprine and mycophenolate can be used to reduce inflammation in patients with moderate-severe Crohn disease by inhibition of *de novo* purine synthesis, which immune cells (eg, B and T cells) are especially dependent on during proliferation. Both agents inhibit key enzymes in the purine synthesis pathway (which occurs in the cytosol) rather than inhibiting transcription factors.

(Choice C) Although infliximab can be used to induce remission in patients with moderate-severe Crohn disease, it is a monoclonal antibody that reduces inflammation by binding to and inhibiting the proinflammatory effects of tumor necrosis factor-alpha (TNF-alpha), a cytokine that is primarily found extracellularly.

(Choice D) Methotrexate and its breakdown products are folic acid analogues that can reduce inflammation by competitively inhibiting multiple folate-dependent enzymes rather than inhibiting transcription factors.

Educational objective:
Budesonide, like other glucocorticoids, reduces inflammation by binding to a cytosolic receptor, translocating into the nucleus, and inhibiting proinflammatory transcription factors such as nuclear factor-kappa-B (NF-κB). It is especially useful in reducing transmural bowel inflammation in patients with Crohn disease because it has high topical potency and limited systemic adverse effects due to high first-pass metabolism.

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Pharmacology	Allergy & Immunology	Corticosteroids
Subject	System	Topic

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A 12-year-old girl is being evaluated for recurrent episodes of self-limited colicky abdominal pain and nausea lasting several days. She was also recently hospitalized for an episode of difficulty breathing. The patient has no significant past medical history, but her mother has a history of attacks of severe abdominal pain and diarrhea. Physical examination is unremarkable. Laboratory evaluation reveals decreased serum complement C4 and C1 esterase inhibitor levels. Which of the following drugs is contraindicated in this patient?

A. Captopril
B. Furosemide
C. Methotrexate
D. Metoprolol
E. Penicillin

Submit

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- ✓ A. Captopril (62%)
- B. Furosemide (4%)
- C. Methotrexate (19%)
- D. Metoprolol (4%)
- E. Penicillin (9%)

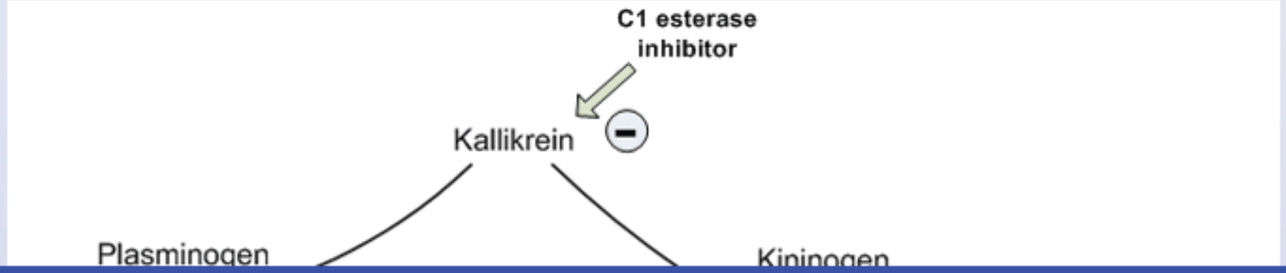
Omitted
Correct answer
A

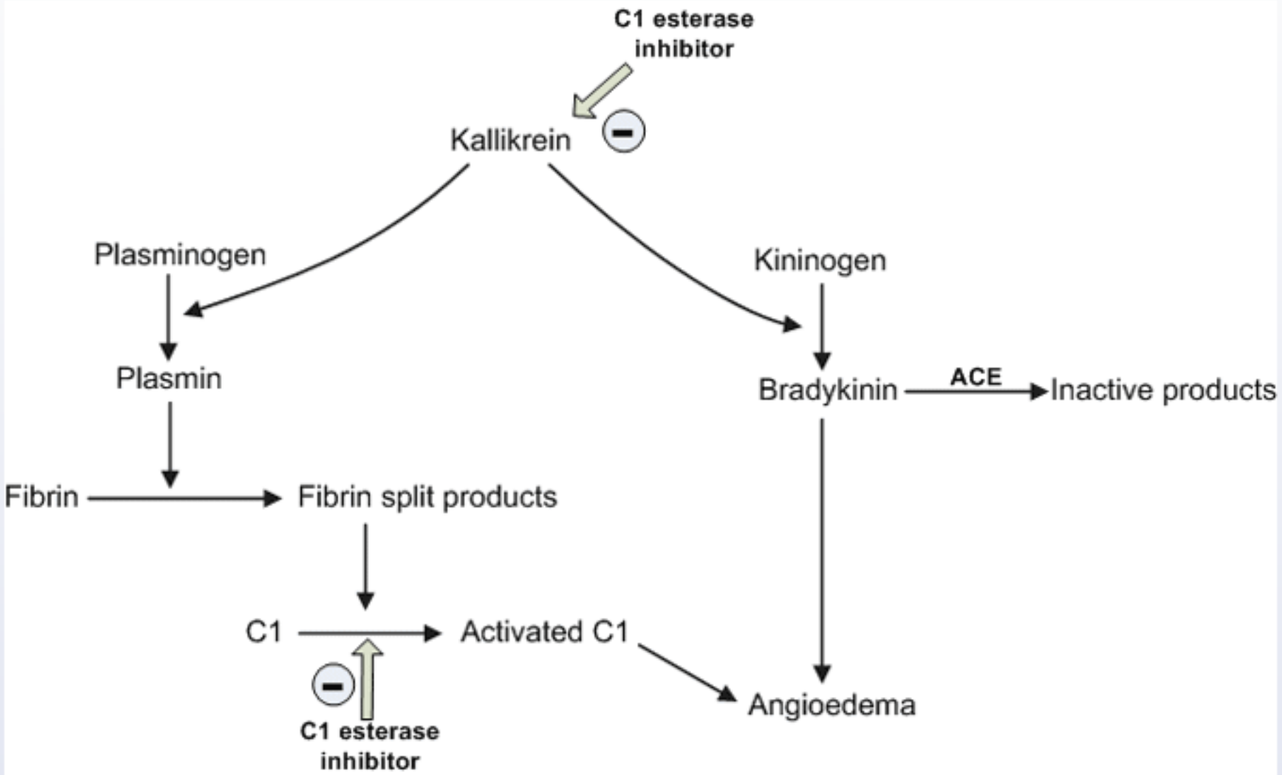
62%
Answered correctly

01 sec
Time Spent

05/19/2020
Last Updated

Explanation





Low serum levels of C1 esterase inhibitor (and its substrate C4) are diagnostic of **hereditary angioedema**, an inherited autosomal dominant condition that causes episodes of painless, non-pitting, well-circumscribed edema. The face, neck, lips, and tongue are most commonly affected, but internal organs may also be involved. Angioedema affecting the tracheobronchial tree can cause respiratory obstruction and is potentially fatal. Angioedema of the gastrointestinal tract manifests with abdominal pain, vomiting, and diarrhea.

Normally, **C1 esterase inhibitor** suppresses activation of the C1 complement component and therefore the rest of the classic complement pathway. It also inactivates **kallikrein**, which catalyzes the conversion of kininogen to bradykinin. In **hereditary** angioedema, low C1 esterase inhibitor activity leads to an increase in active kallikrein and bradykinin levels. **Bradykinin** (along with C3a and C5a) mediate angioedema by increasing vasodilation and vascular permeability.

C1 esterase inhibitor

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Angioedema may also occur as a side effect of **angiotensin-converting enzyme (ACE) inhibitor** medications. ACE normally catalyzes the conversion of angiotensin I into angiotensin II. ACE also converts bradykinin into inactive metabolites. ACE inhibitors can therefore lead to **bradykinin accumulation**. These medications should **not** be used in patients with hereditary angioedema as they may precipitate disease episodes.

(Choice B) Furosemide can cause hypokalemia, hyperuricemia, and hypovolemia. Ototoxicity may occur if furosemide is used with aminoglycosides.

(Choice C) Methotrexate can cause hepatitis, pulmonary fibrosis, and bone marrow suppression.

(Choice D) Metoprolol is a selective β1-adrenergic blocker with few side effects. It may cause heart block in patients with conduction system disease and bronchoconstriction in asthmatic patients (rare due to β1 selectivity but can still occur).

(Choice E) The most common side effect of penicillin is hypersensitivity.

Educational objective:
Angioedema can be hereditary (autosomal dominant) or acquired (associated with angiotensin-converting enzyme [ACE] inhibitor treatment). In hereditary angioedema, low C1 esterase inhibitor activity leads to increases in bradykinin activity. ACE inhibitors should not be used in these patients.

A 50-year-old woman comes to the office due to cough, shortness of breath, fatigue, and weight loss. The patient does not use tobacco or alcohol. Blood pressure is 110/70 mm Hg, pulse is 88/min and regular, and oxygen saturation on room air is 96%. Lung examination reveals scattered crackles. Serum calcium levels are elevated. Imaging studies reveal mediastinal fullness and diffuse, bilateral, ground-glass lung opacities. Biopsy of the lung lesions shows granulomas with multinucleated giant cells; no microorganisms or particulates are present. Appropriate pharmacotherapy is initiated. At follow-up a few days later, the symptoms have improved but blood glucose is elevated. Which of the following additional changes is most likely present in this patient due to her treatment?

A. Decreased production of IL-10

B. Impaired migration of neutrophils to inflammatory sites

C. Increased apoptosis of neutrophils

D. Increased expression of IL-1

E. Increased formation of 1,25-dihydroxyvitamin D

F. Increased production of prostaglandins

Submit

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- A. Decreased production of IL-10 (7%)
- ✓ B. Impaired migration of neutrophils to inflammatory sites (72%)
- C. Increased apoptosis of neutrophils (6%)
- D. Increased expression of IL-1 (2%)
- E. Increased formation of 1,25-dihydroxyvitamin D (7%)
- F. Increased production of prostaglandins (3%)

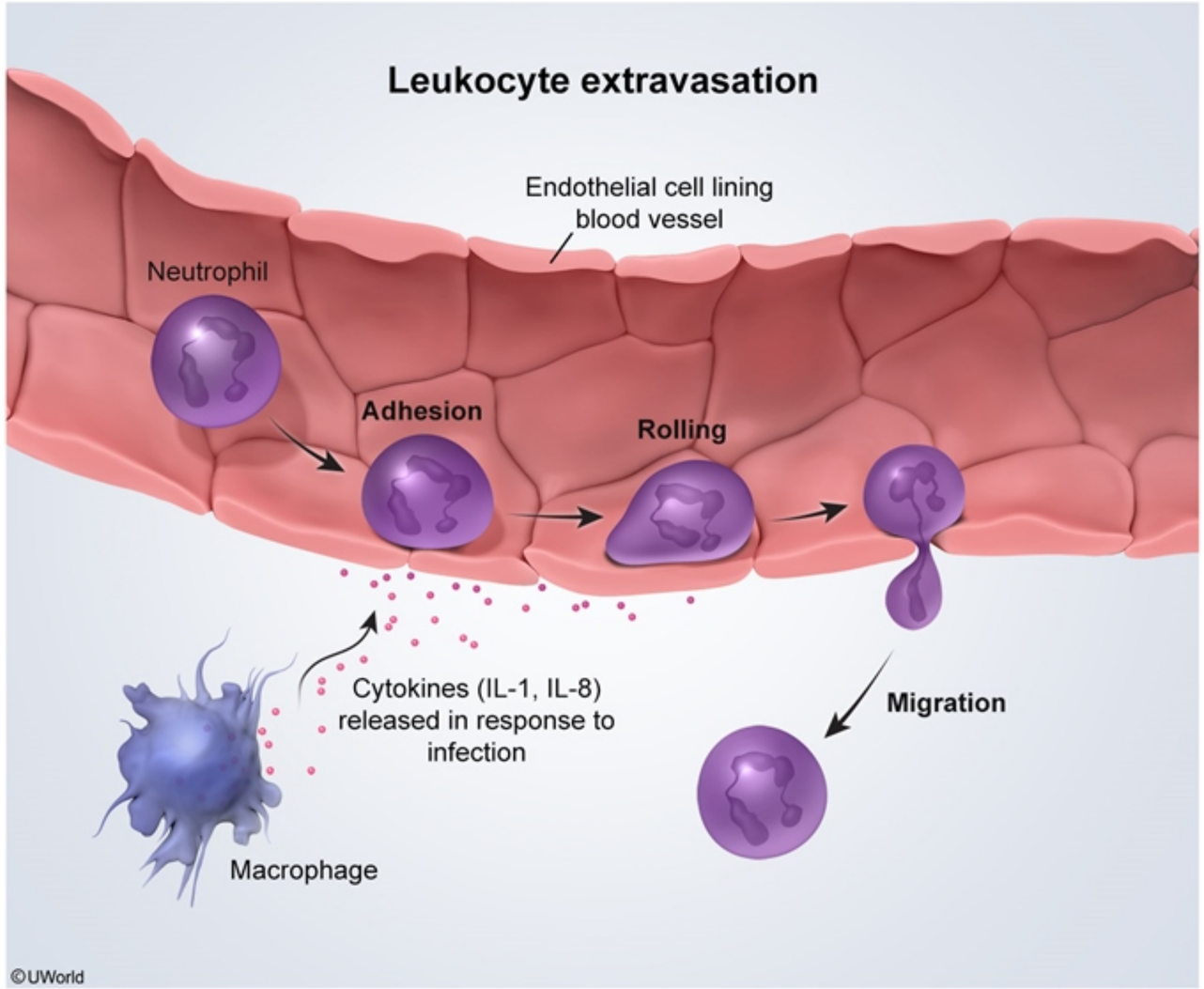
Omitted
Correct answer
B

72%
Answered correctly

01 sec
Time Spent

05/07/2020
Last Updated

Explanation



This patient with cough, **shortness of breath**, and fatigue has multiple findings characteristic of granulomatous inflammation in **sarcoidosis**,

This patient with cough, **shortness of breath**, and fatigue has multiple findings characteristic of granulomatous inflammation in **sarcoidosis**, including the following:

- Elevated serum calcium due to increased 1,25-dihydroxyvitamin D production by activated macrophages
- Mediastinal and hilar adenopathy
- Granulomas (noncaseating) with multinucleated giant cells and no microorganisms on lung biopsy

Glucocorticoids are commonly used as initial therapy in patients with sarcoidosis because of their ability to **reduce inflammation**, improving symptoms and limiting end-organ damage while having relatively minor adverse effects (eg, weight gain, **glucose intolerance**) with short term use. Glucocorticoids improve sarcoidosis symptoms by decreasing transcription of proinflammatory genes, leading to reduced activation of lymphocytes and macrophages with **decreased** expression of cytokines necessary for granuloma formation (eg, **IL-1**, interferon-gamma) **(Choice D)**.

Glucocorticoids also **impair neutrophil** margination, extravasation, and **migration** to inflammatory sites by reducing adhesion molecule expression on neutrophils (eg, L selectin) and endothelial cells and limiting production of cytokines (eg, IL-8) that promote neutrophil emigration. The result is increased circulating levels of neutrophils (ie, **neutrophilia**).

In addition to these changes, glucocorticoids have a variety of other effects on immune function, as follows:

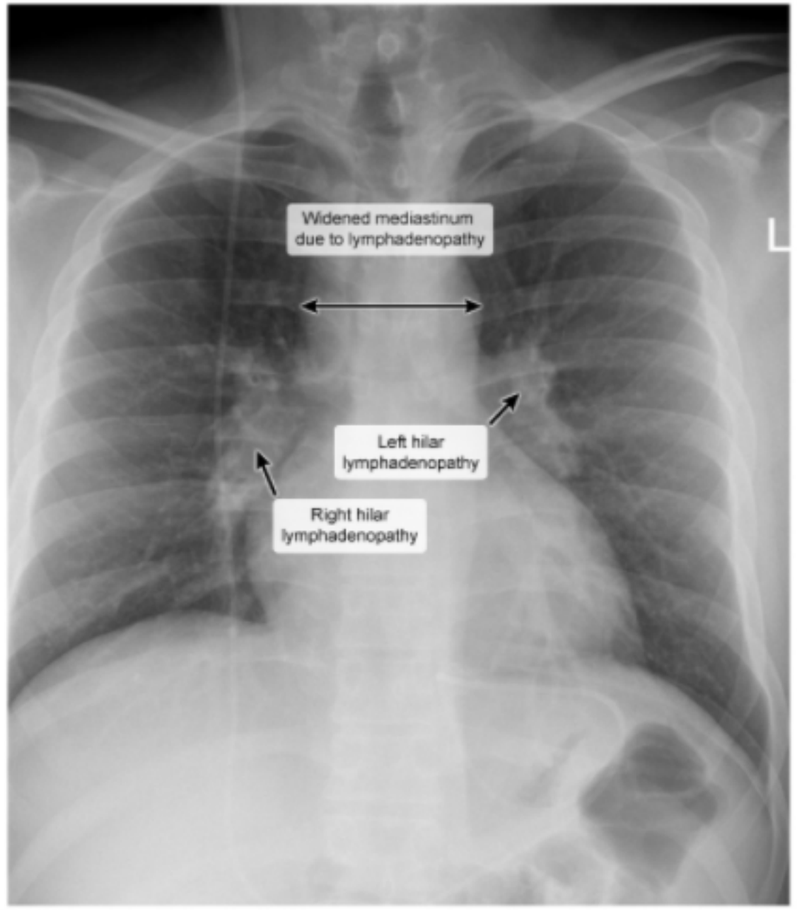
- Increased production of anti-inflammatory cytokines (eg, IL-10) **(Choice A)**
- Decreased apoptosis of neutrophils, reinforcing neutrophilia **(Choice C)**
- Promoting apoptosis of eosinophils, monocytes, and lymphocytes, decreasing circulating levels
- Reduced macrophage activation (decreasing overall 1,25-dihydroxyvitamin D synthesis) **(Choice E)**
- Decreased production of prostaglandins and leukotrienes through the inhibition of phospholipase A2 **(Choice F)**

Educational objective:
Glucocorticoids have a variety of effects that can be useful in reducing inflammation and limiting end-organ damage in inflammatory diseases (eg, sarcoidosis). These include decreased proinflammatory cytokine (IL-1, interferon-gamma) production, increased anti-inflammatory cytokine (eg,

This patient with cough, **shortness of breath**, and fatigue has multiple findings characteristic of granulomatous inflammation in **sarcoidosis**.

Exhibit Display

Sarcoidosis with mediastinal and hilar lymphadenopathy



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This patient with cough, **shortness of breath**, and fatigue has multiple findings characteristic of granulomatous inflammation in **sarcoidosis**.

Exhibit Display

Noncaseating granuloma

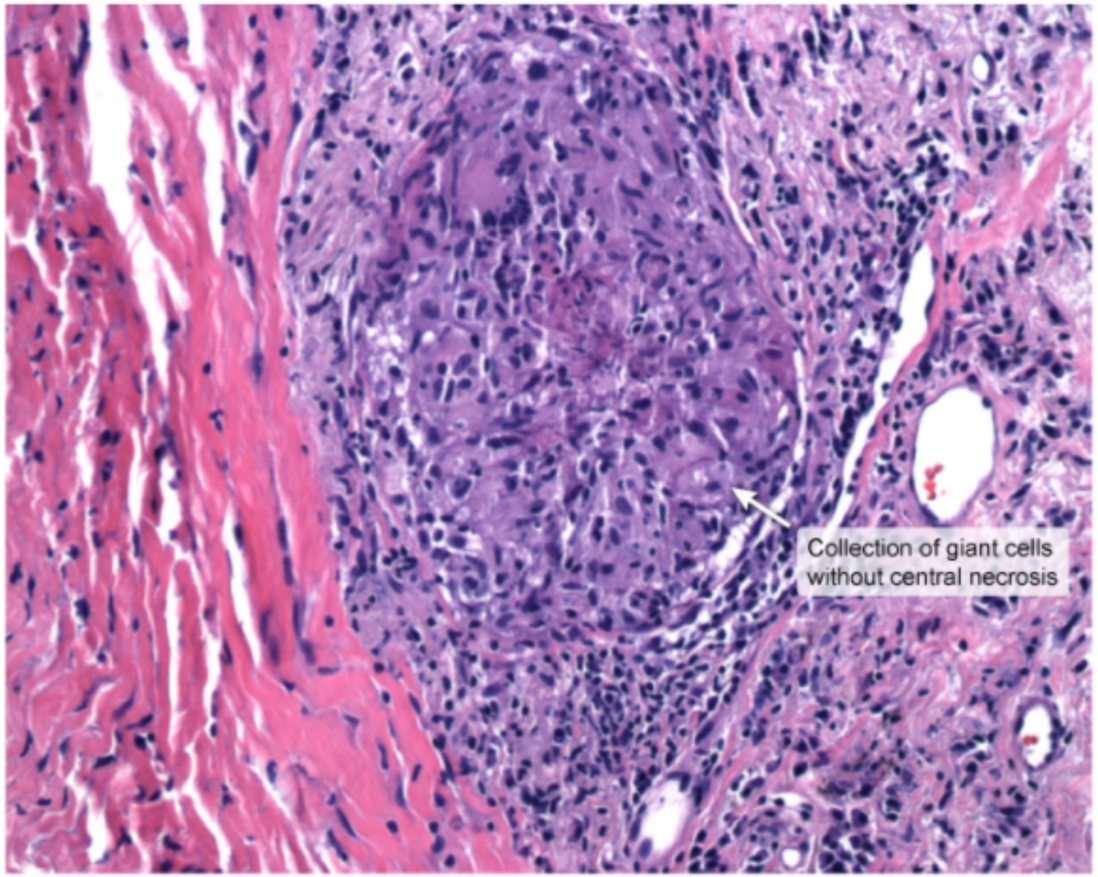

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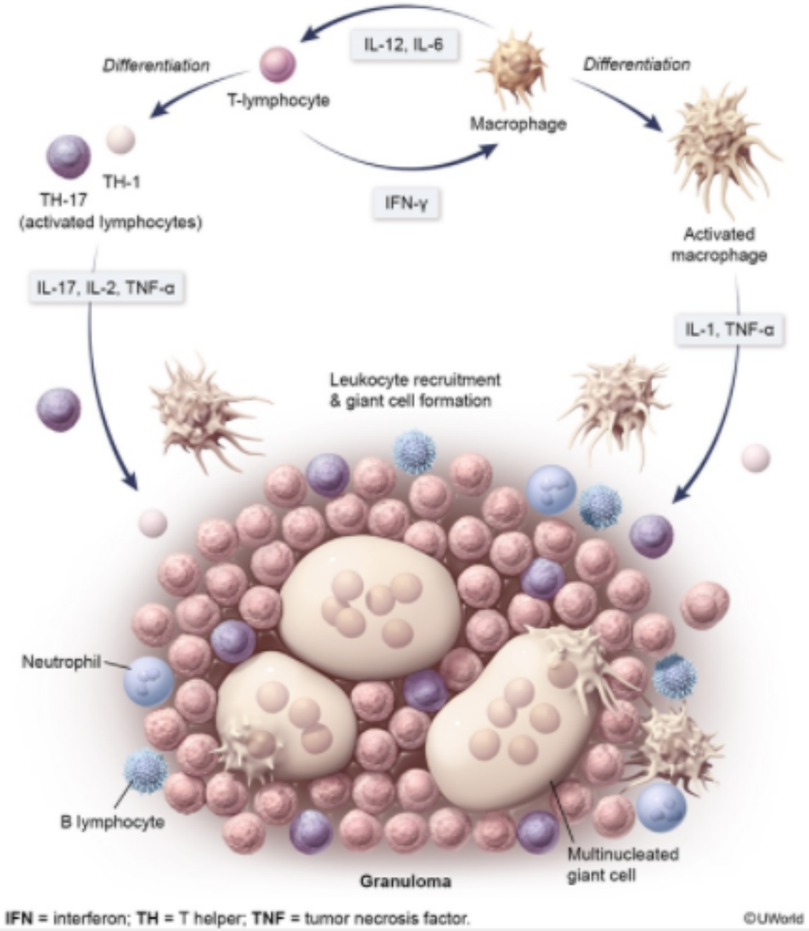
Exhibit Display



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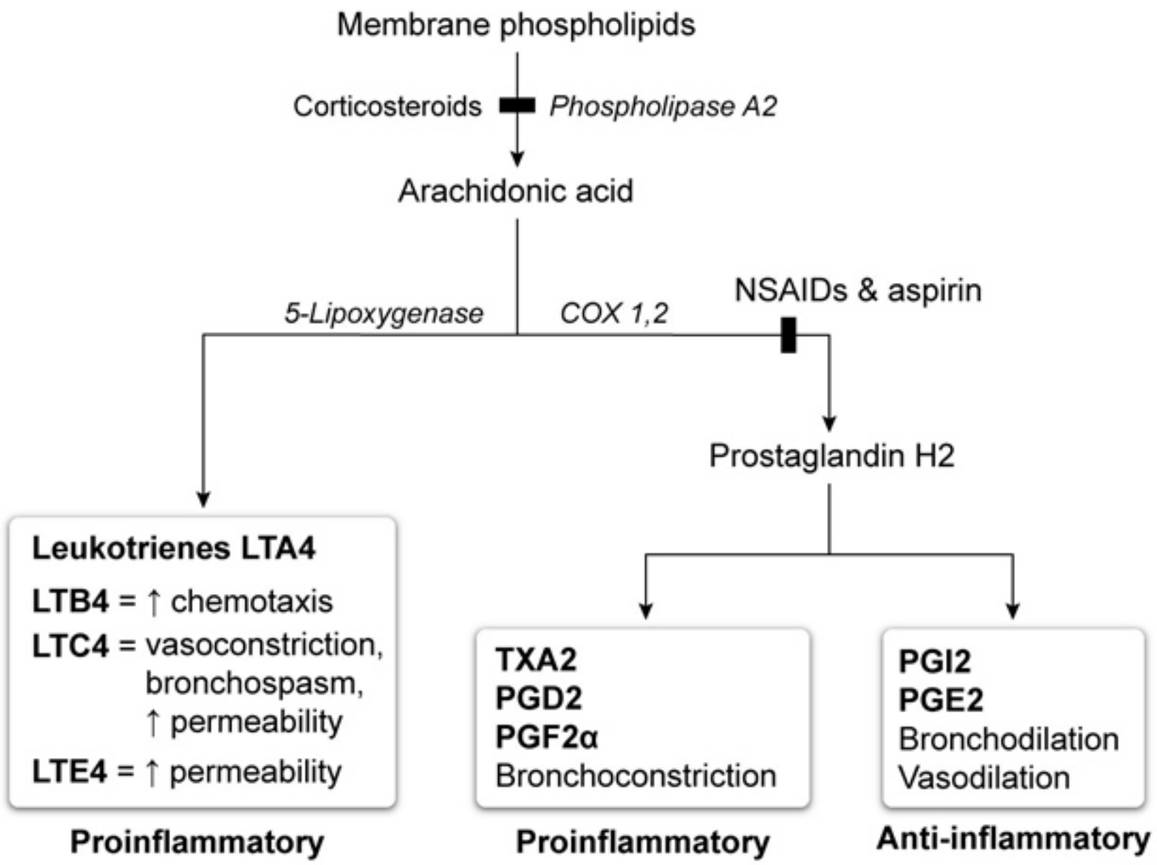

COX = cyclooxygenase-2; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **PG** = prostaglandin; **TXA** = tranexamic acid.

Zoom In Zoom Out Reset Add To Flash Card

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A 62-year-old woman undergoes hip replacement surgery. The patient has a history of advanced hip osteoarthritis that limits her daily activities. She has no other medical conditions and no known drug allergies. After appropriate preoperative evaluation, total hip arthroplasty is performed under general anesthesia. The intraoperative course is uncomplicated, and after recovery from anesthesia, patient-controlled intravenous morphine is started for pain control. Several minutes later, the patient reports generalized itching. Physical examination reveals hypotension, tachycardia, and mild bilateral wheezing but no rashes. Which of the following drug effects is most likely responsible for this patient's current condition?

A. Decreased myocardial contractility

B. Decreased sympathetic output

C. Direct mast cell degranulation

D. Formation of drug-IgE complexes

E. Increased 5-lipoxygenase activity

Submit

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- A. Decreased myocardial contractility (1%)
- B. Decreased sympathetic output (4%)
- ✓ C. Direct mast cell degranulation (72%)
- D. Formation of drug-IgE complexes (17%)
- E. Increased 5-lipoxygenase activity (4%)

Omitted
Correct answer
C

72%
Answered correctly

02 secs
Time Spent

05/30/2020
Last Updated

Explanation

Opioids (eg, morphine) can generate a **pseudoallergic** response by **directly stimulating mast cell degranulation**, releasing **histamine** and other vasoactive mediators. This **nonimmunologic** reaction can cause itching, urticarial rash, wheezing, hypotension, and tachycardia that closely mimic true IgE-mediated type 1 hypersensitivity (eg, anaphylaxis). However, true IgE-mediated allergic reaction is rare with opioids **(Choice D)**, and suggestive symptoms rarely indicate the need to avoid opioids altogether. Because direct mast cell degranulation tends to be

Opioids (eg, morphine) can generate a **pseudoallergic** response by **directly stimulating mast cell degranulation**, releasing **histamine** and other vasoactive mediators. This **nonimmunologic** reaction can cause itching, urticarial rash, wheezing, hypotension, and tachycardia that closely mimic true IgE-mediated type 1 hypersensitivity (eg, anaphylaxis). However, true IgE-mediated allergic reaction is rare with opioids **(Choice D)**, and suggestive symptoms rarely indicate the need to avoid opioids altogether. Because direct mast cell degranulation tends to be most prominent with relatively low-potency opioids (eg, morphine, meperidine), a relatively high-potency opioid (eg, fentanyl) is usually better tolerated.

Other drugs that can have a similar **non-IgE-mediated effect** on mast cell degranulation include vancomycin (ie, red man syndrome) and radioiodine contrast.

(Choice A) Halothane, an inhalation anesthetic, is rarely used but can cause hypotension via direct suppression of myocardial contractility. It is not associated with itching and wheezing.

(Choice B) Because pain increases sympathetic output, opioid analgesia can reduce sympathetic output and thus decrease heart rate and blood pressure. However, this does not explain the itching and wheezing.

(Choice E) Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase, which leads to increased 5-lipoxygenase activity. This effect can precipitate bronchoconstriction and wheezing due to increased production of leukotrienes (ie, NSAID-exacerbated respiratory disease); however, itching and hypotension are not expected.

Educational objective:
Opioids (eg, morphine) can generate a pseudoallergic response by directly activating mast cells to stimulate degranulation, releasing histamine and other vasoactive mediators. This nonimmunologic reaction can cause itching, urticarial rash, wheezing, hypotension, and tachycardia that closely mimic true IgE-mediated type 1 hypersensitivity. However, true IgE-mediated allergic reaction is rare with opioids.

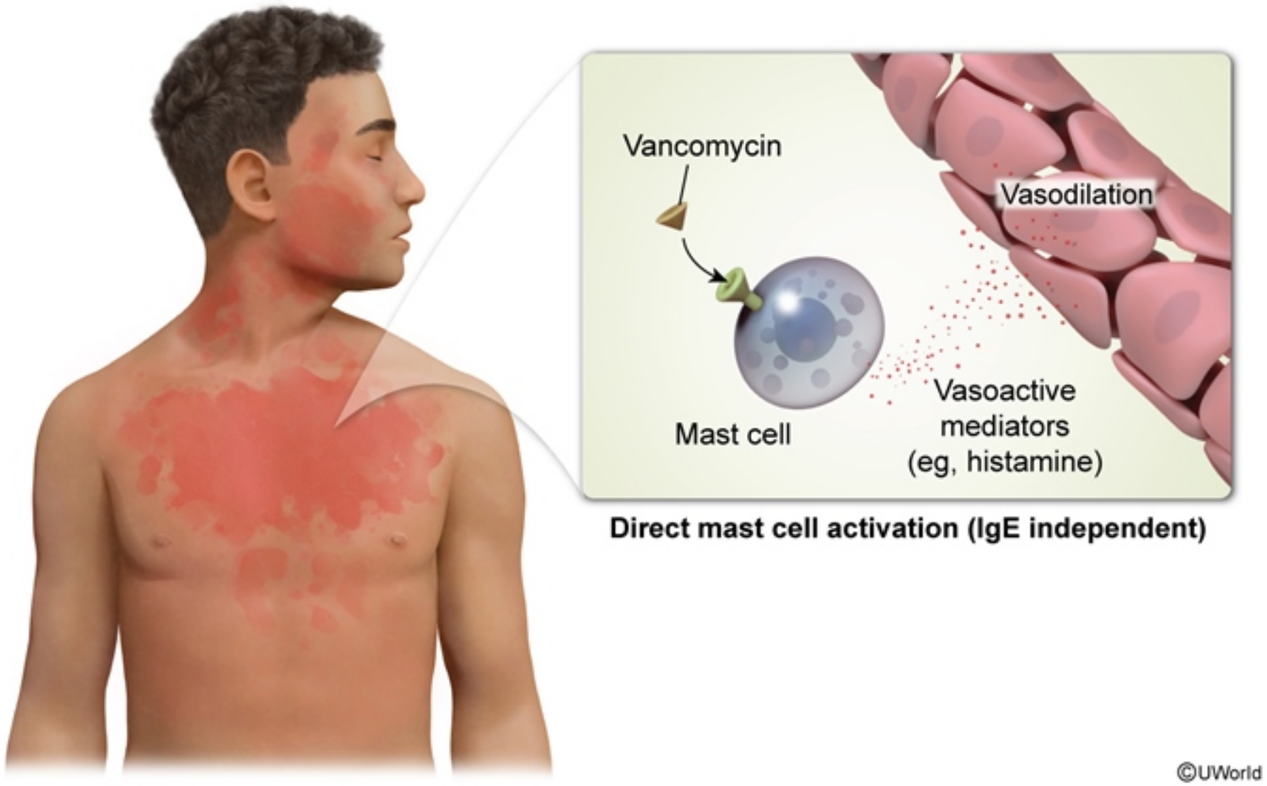
References

- Drug-Induced Pseudoallergy: A Review of the Causes and Mechanisms.

Pharmacology	Allergy & Immunology	Opioids
Subject	System	Topic

Exhibit Display

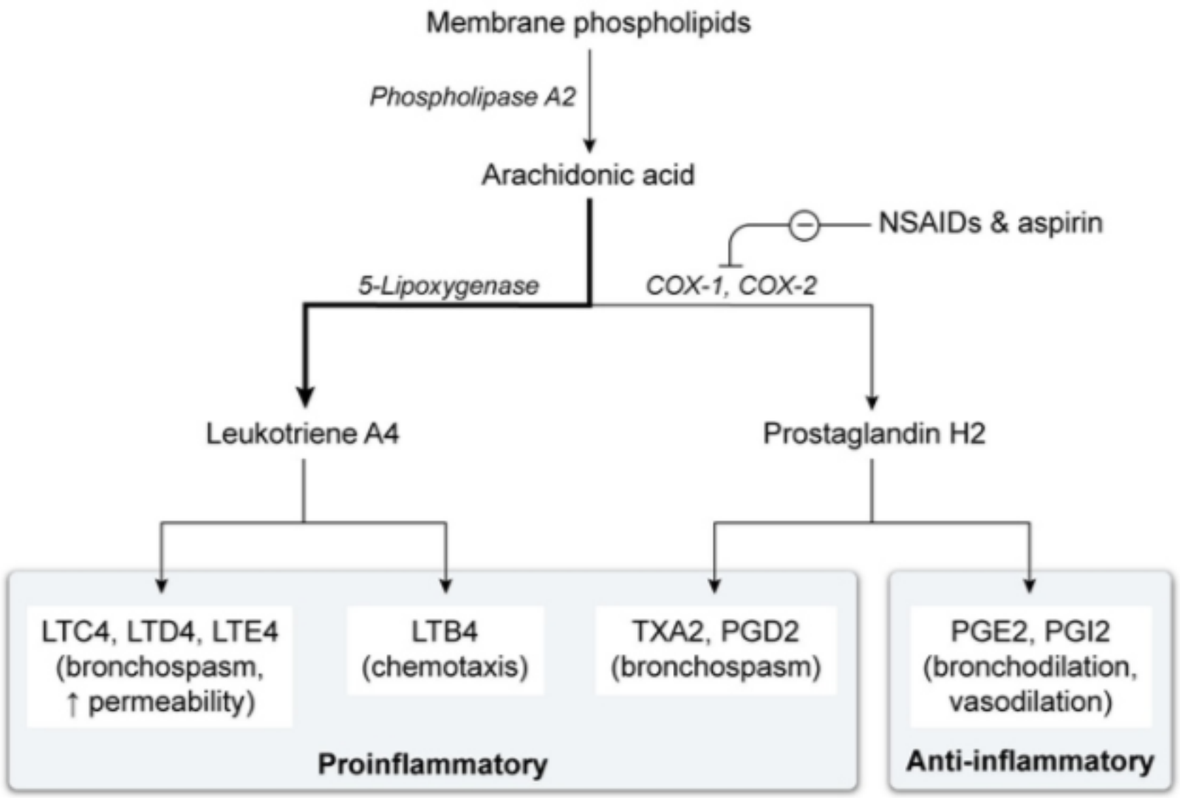
Red man syndrome



Direct mast cell activation (IgE independent)

Exhibit Display

Arachidonic acid pathway in NSAID-exacerbated respiratory disease



COX = cyclooxygenase; **LT** = leukotriene; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **PG** = prostaglandin; **TX** = thromboxane.

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Subject System Topic

A 32-year-old man comes to the clinic for follow-up due to Crohn disease. The patient was initially diagnosed 3 years ago and achieved disease remission following a course of high-dose glucocorticoids. He remained in remission until 2 months ago, when he experienced an acute flare of diarrhea and abdominal pain that required a brief hospitalization and another course of high-dose glucocorticoids. The patient completed a prescribed glucocorticoid taper earlier this week and says that his symptoms have returned to "about normal." Azathioprine maintenance therapy is started to help prevent future flares. Which of the following most accurately describes the expected effects of this new medication on immune function?

	B-lymphocyte count	T-lymphocyte count	Immunoglobulin level	IL-2 activity
A.	↓	No effect	↓	No effect
B.	↓	↓	↓	↓
C.	No effect	↓	No effect	↓
D.	↓	↓	↑	↑
E.	↑	↑	↓	↓

Submit

A 32-year-old man comes to the clinic for follow-up due to Crohn disease. The patient was initially diagnosed 3 years ago and achieved disease remission following a course of high-dose glucocorticoids. He remained in remission until 2 months ago, when he experienced an acute flare of diarrhea and abdominal pain that required a brief hospitalization and another course of high-dose glucocorticoids. The patient completed a prescribed glucocorticoid taper earlier this week and says that his symptoms have returned to "about normal." Azathioprine maintenance therapy is started to help prevent future flares. Which of the following most accurately describes the expected effects of this new medication on immune function?

	B-lymphocyte count	T-lymphocyte count	Immunoglobulin level	IL-2 activity
A. (7%)	↓	No effect	↓	No effect
✓ B. (69%)	↓	↓	↓	↓
C. (20%)	No effect	↓	No effect	↓
D. (2%)	↓	↓	↑	↑
E. (0%)	↑	↑	↓	↓

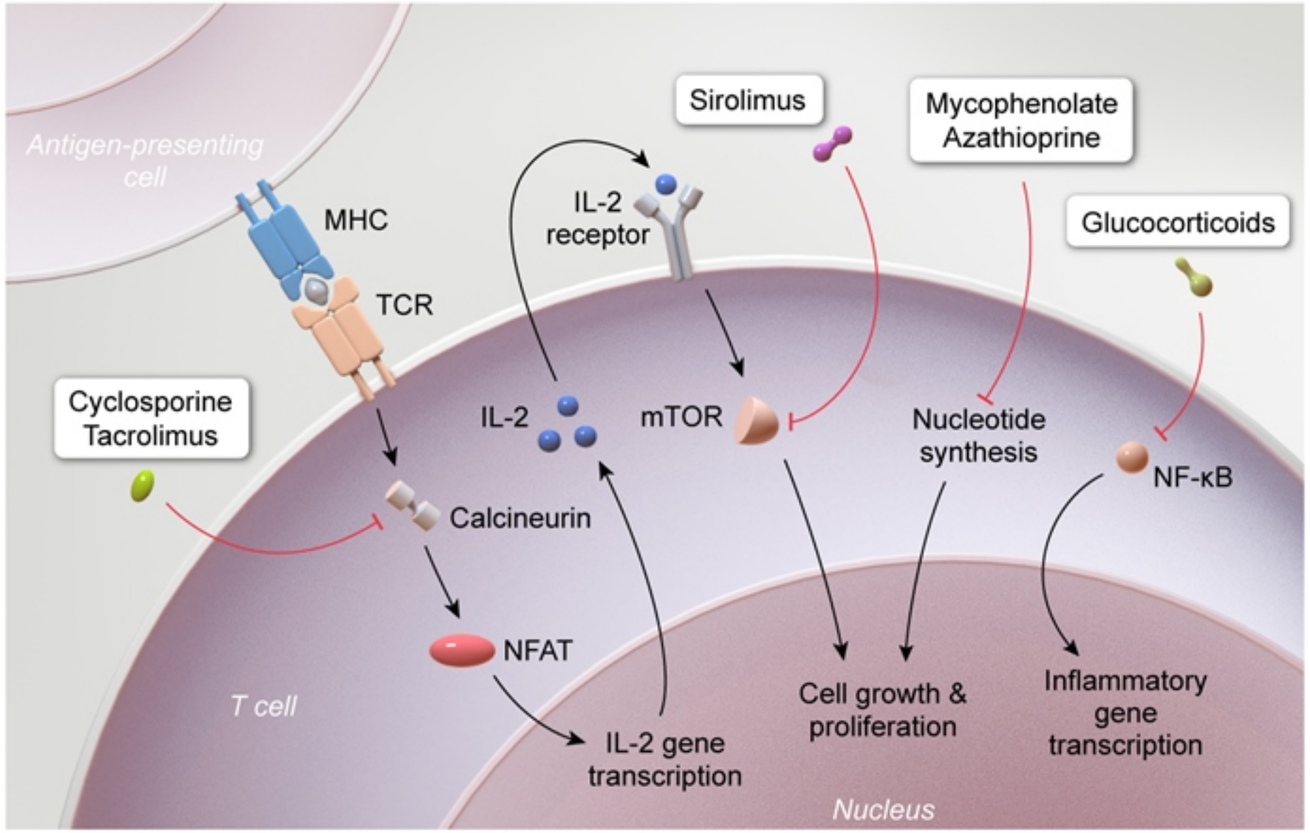
Omitted
Correct answer
B

69%
Answered correctly

03 secs
Time Spent

04/22/2020
Last Updated

Mechanism of action of common immunosuppressants



MHC = major histocompatibility complex; **mTOR** = mammalian target of rapamycin; **NFAT** = nuclear factor of activated T cells; **NF-κB** = nuclear factor kappa-light-chain-enhancer of activated B cells; **TCR** = T-cell receptor.

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Azathioprine is an immunosuppression drug sometimes used in the treatment of autoimmune disease (eg, inflammatory bowel disease) and the prevention of organ transplant rejection. It generates 6-thioguanine metabolites that both **inhibit** an early step in **de novo purine synthesis** and act as false purine nucleotides that **disrupt DNA and RNA replication**. These effects are nonspecific and affect the proliferation of all rapidly dividing cells, including hematopoietic cells. Therefore, there is **reduced proliferation** of both **B and T lymphocytes**. The reduced number of

factor kappa-light-chain-enhancer of activated B cells; TCR = T-cell receptor.

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Common adverse effects of azathioprine include **pancytopenia** (ie, anemia, leukopenia, and thrombocytopenia) and increased susceptibility to infection.

(Choice A) Rituximab is a monoclonal antibody sometimes used to treat autoimmune disease and hematologic malignancy. It binds to CD20 receptors on B lymphocytes, resulting in apoptosis; the B lymphocyte count and immunoglobulin levels are reduced, but there is minimal effect on T lymphocytes.

(Choice C) Muromonab is a monoclonal antibody sometimes used to prevent organ transplant rejection. It binds to CD3 receptors on T cells to trigger apoptosis, reducing T-lymphocyte count and IL-2 activity. There is no direct effect on B lymphocytes, but B lymphocyte activity is reduced due to decreased activation by T lymphocytes.

(Choices D and E) Azathioprine reduces the quantity and activity of both B and T lymphocytes. Immunoglobulin levels are usually directly related to B-lymphocyte count, and IL-2 activity is usually directly related to T-lymphocyte count; that is, if lymphocyte counts are low, immunoglobin levels and IL-2 activity are also low.

Educational objective:
Azathioprine is an immunosuppression drug that inhibits purine nucleotide synthesis and incorporates false purine nucleotides into DNA and RNA. These effects reduce the proliferation and activity of both B and T lymphocytes.

References

- Azathioprine.

Pharmacology Allergy & Immunology Azathioprine

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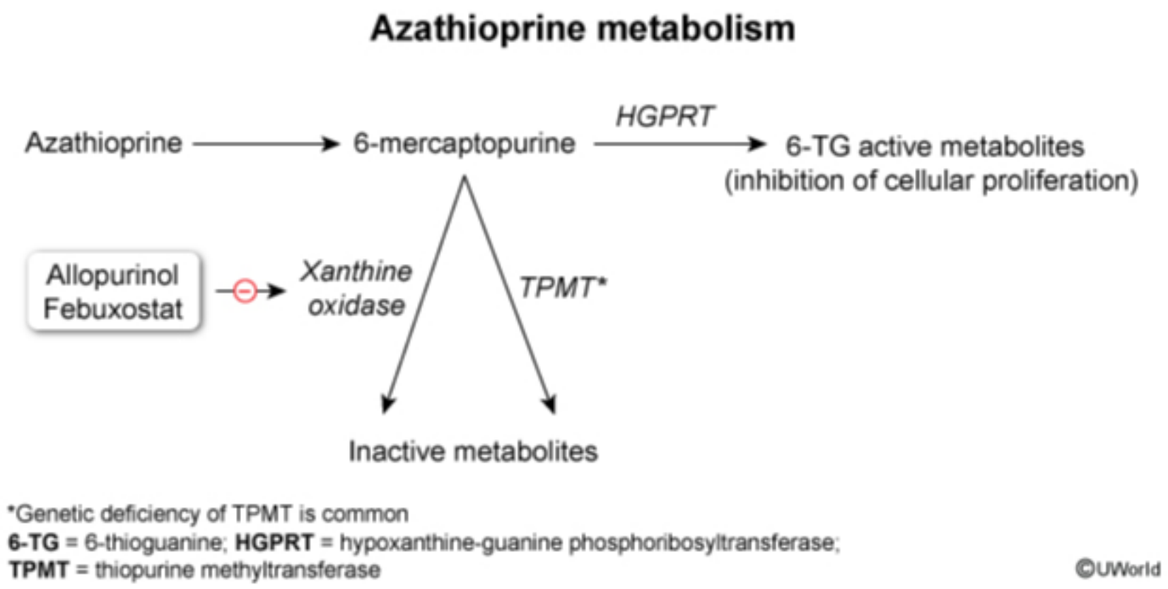

*Genetic deficiency of TPMT is common
6-TG = 6-thioguanine; **HGPRT** = hypoxanthine-guanine phosphoribosyltransferase;
TPMT = thiopurine methyltransferase

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Pharmacology Allergy & Immunology Azathioprine

A 57-year-old male with suspected bacterial pneumonia is admitted to the hospital and given ceftriaxone and azithromycin for treatment. Soon after the first dose of ceftriaxone, he complains of difficulty breathing, abdominal cramps, and lightheadedness. His current blood pressure is 70/50 mmHg, while his heart rate is 120/min. Physical examination reveals a diffuse maculopapular rash. Which of the following drugs should be administered next to this patient?

A. Corticosteroids
B. Epinephrine
C. Norepinephrine
D. Dobutamine
E. Diphenhydramine

Submit

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A. Corticosteroids (11%)
✓ B. Epinephrine (65%)
C. Norepinephrine (7%)
D. Dobutamine (4%)
E. Diphenhydramine (10%)

Omitted
Correct answer
B

65%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

Dyspnea, hypotension, and tachycardia soon after administration of β-lactam antibiotics are suggestive of anaphylactic shock. Hypotension occurs in anaphylactic shock secondary to collapse of peripheral vascular resistance, increases in vascular permeability, and leakage of capillary fluid. Stimulation of the smooth muscle tone within the bronchial wall, along with an increase in bronchial secretion, accounts for the dyspnea seen in anaphylaxis. Skin symptoms (urticaria and angioedema) may occur secondary to vasodilatation and increased vascular permeability of skin capillaries. Increases in GI smooth muscle tone may result in vomiting, abdominal cramps, and diarrhea.

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Epinephrine is the drug of choice for the treatment of anaphylactic shock due to its ability to reverse all of the pathophysiologic mechanisms of anaphylaxis. Stimulation of α1 receptors counteracts the vasodilatation of cutaneous and viscera vasculature, thus increasing blood pressure. Epinephrine-mediated increases in cardiac contractility (β1 effect) and cardiac output also increase blood pressure and improve peripheral perfusion. Epinephrine-induced stimulation of β2 receptors results in bronchodilatation, making it also a popular choice for the treatment of severe asthmatic reactions.

(Choice A) Steroids inhibit inflammation by reducing capillary permeability and suppressing neutrophil activity. Steroids also inhibit phospholipase A2, resulting in decreased formation of prostaglandin inflammatory mediators. Because steroids anti-inflammatory effects are not acute, they are not effective in the acute treatment of life-threatening anaphylaxis. Epinephrine should be given prior to steroids and antihistamines in the treatment of anaphylaxis.

(Choice C) Norepinephrine has a predominantly alpha-1 adrenergic effect; thus, it can cause intense vasoconstriction, which may limit cardiac output. Furthermore, it has little effect on the beta-2 adrenoceptor, so it has little or no bronchodilator action.

(Choice D) Dobutamine is a synthetic drug with primary beta-1 adrenergic action that can cause an increased cardiac output without the other effects of epinephrine.

(Choice E) Diphenhydramine is a first generation antihistamine drug that competitively inhibits peripheral H1 receptors in the GI tract, blood vessels, and respiratory tract. Diphenhydramine may be used for the treatment of anaphylaxis after the patient is stabilized with epinephrine.

Educational Objective:
Anaphylactic shock is characterized by vasodilatation, increased vascular permeability, and bronchoconstriction. Epinephrine counteracts these physiological mechanisms and is the drug of choice for the treatment of anaphylaxis.

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Pharmacology	Allergy & Immunology	Anaphylaxis
Subject	System	Topic

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A 62-year-old woman is admitted to the hospital for a living-donor kidney transplant. She has a history of end-stage kidney disease due to diabetic nephropathy and has been undergoing hemodialysis for the last 2 years. The transplant surgery is performed without complication, and the patient demonstrates good urine output afterward. To help prevent rejection, she is given a medication that inhibits the conversion of inosine monophosphate to guanosine monophosphate primarily in lymphocytes, causing reduced proliferation of activated lymphocytes. Which of the following medications is most likely being used in this patient?

A. Azathioprine
B. Mycophenolate
C. Prednisone
D. Sirolimus
E. Tacrolimus

Submit

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- A. Azathioprine (25%)
- ✓ B. Mycophenolate (66%)
- C. Prednisone (1%)
- D. Sirolimus (3%)
- E. Tacrolimus (3%)

Omitted
Correct answer
B

66%
Answered correctly

03 secs
Time Spent

04/22/2020
Last Updated

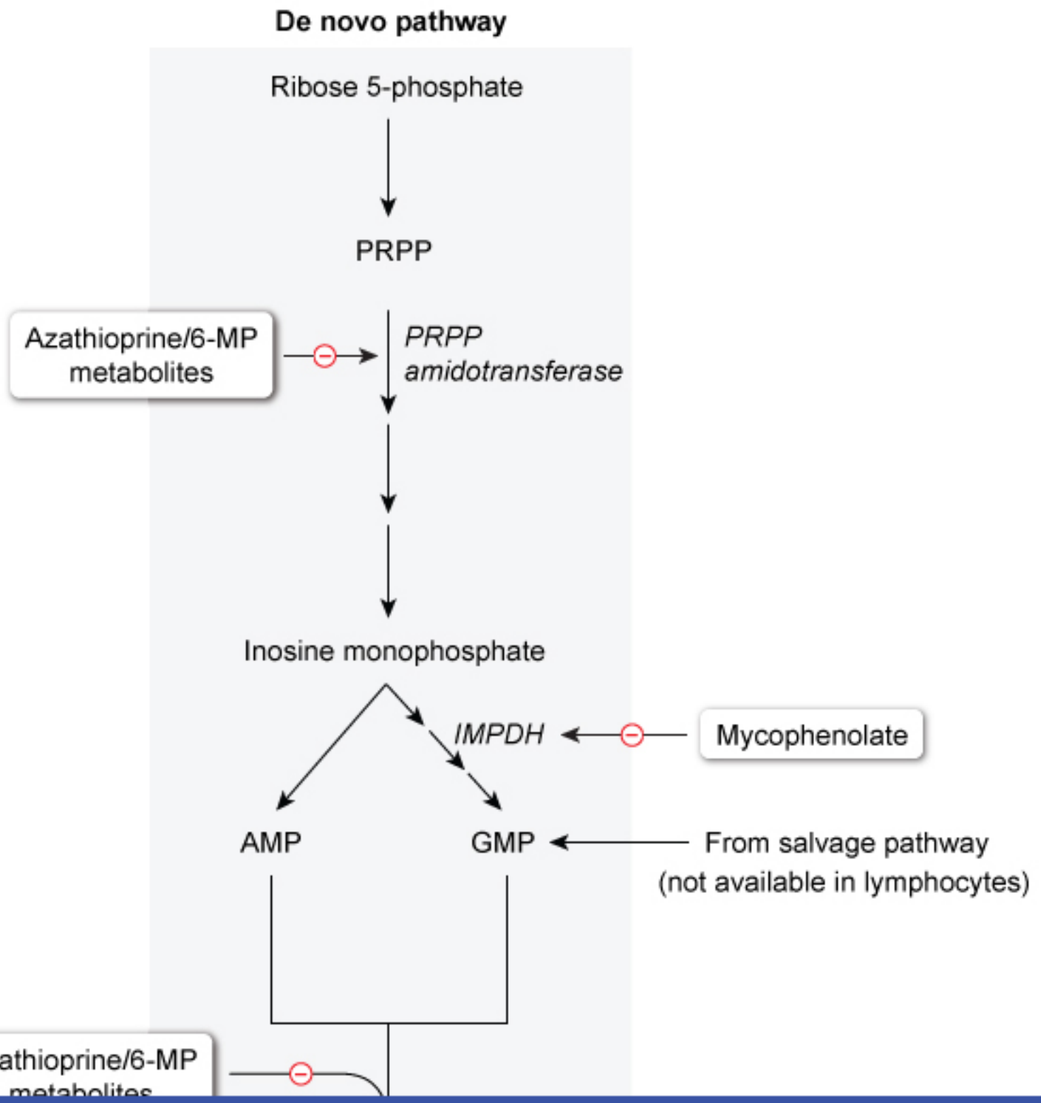
Explanation

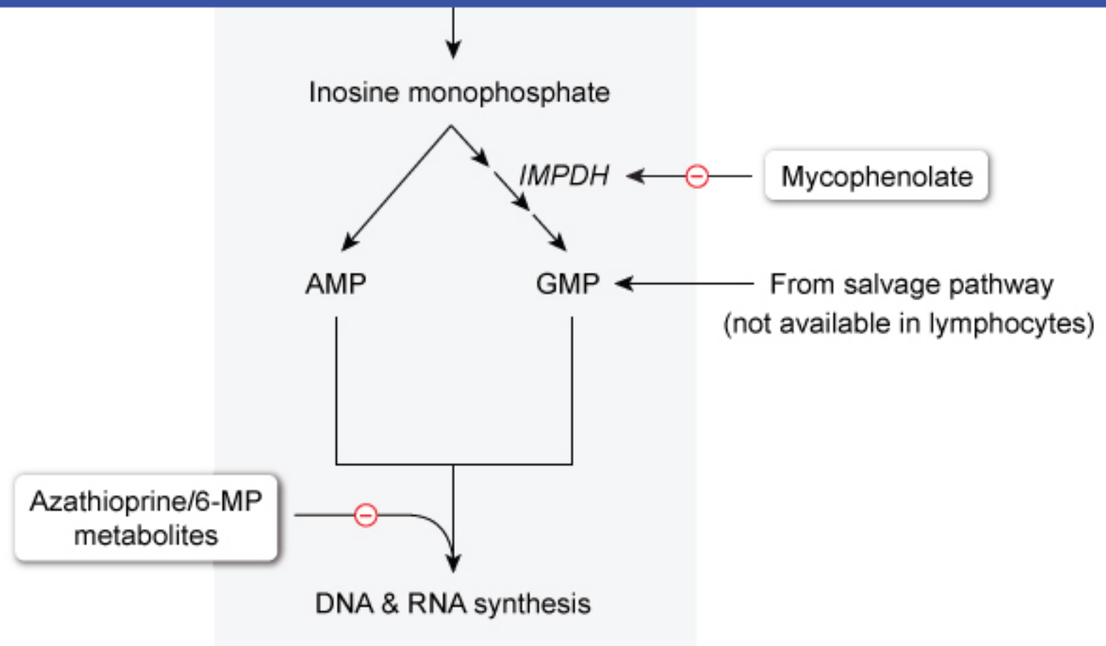
Immunosuppressant inhibition of purine synthesis

De novo pathway

Ribose 5-phosphate

Immunosuppressant inhibition of purine synthesis





6-MP = 6-mercaptopurine; **AMP** = adenosine monophosphate, **GMP** = guanosine monophosphate; **IMPDH** = inosine monophosphate dehydrogenase; **PRPP** = phosphoribosyl pyrophosphate.

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Mycophenolate is an immunosuppression drug used to prevent organ transplant rejection. It functions via the **inhibition of inosine 5'-monophosphate dehydrogenase** (IMPDH), an enzyme in the **de novo purine synthesis** pathway. The utility of mycophenolate as an immunosuppressant is aided by its relatively specific suppression of lymphocyte proliferation compared with other hematopoietic cell lines (eg, neutrophils, erythrocytes). This relative lymphocyte specificity is driven by 2 factors:

- Activated **lymphocytes** have a nearly **absent purine salvage pathway** and therefore are mostly **dependent on de novo purine synthesis**. Other hematopoietic cell lines have a more robust purine salvage pathway and can better compensate for inhibition of the de novo pathway.
- There are 2 subtypes of the IMPDH enzyme: Lymphocytes primarily contain type 2 IMPDH, whereas other cell lines contain a greater proportion of type 1. Mycophenolate binds to and inhibits type 2 IMPDH with a higher affinity than type 1.

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- There are 2 subtypes of the IMPDH enzyme: Lymphocytes primarily contain type 2 IMPDH, whereas other cell lines contain a greater proportion of type 1. Mycophenolate binds to and inhibits type 2 IMPDH with a higher affinity than type 1.

Common **adverse effects** of mycophenolate include **lymphopenia** and gastrointestinal disturbances (eg, diarrhea).

(Choice A) Azathioprine produces active metabolites that inhibit an enzyme in the de novo purine synthesis pathway and also act as false nucleotides that incorporate into and disrupt DNA and RNA. Both the de novo and salvage purine synthesis pathways are disrupted, resulting in relatively nonspecific hematopoietic suppression.

(Choice C) Prednisone and other glucocorticoids inhibit NF-kB to decrease the transcription of IL-2 and many other cytokines. These drugs have wide-ranging effects that suppress the function of all leukocyte cell lines.

(Choice D) Sirolimus inhibits the mammalian target of rapamycin (mTOR) to interrupt IL-2 signal transduction and provide relatively specific lymphocyte suppression.

(Choice E) Tacrolimus and cyclosporine inhibit calcineurin to block transcription of IL-2. These drugs provide relatively specific lymphocyte suppression and are the mainstay of therapy for preventing organ transplant rejection.

Educational objective:
Mycophenolate is an immunosuppression drug that inhibits inosine 5'-monophosphate dehydrogenase in the de novo purine synthesis pathway. It provides relatively specific suppression of lymphocyte proliferation, largely because activated lymphocytes lack an established purine salvage pathway that is present in other hematopoietic cell lines.

References

- Mycophenolic acid formulations in adult renal transplantation—update on efficacy and tolerability.
- Calcineurin inhibitor sparing with mycophenolate in kidney transplantation: a systematic review and meta-analysis.

neutrophils, erythrocytes). This relative lymphocyte specificity is driven by 2 factors:

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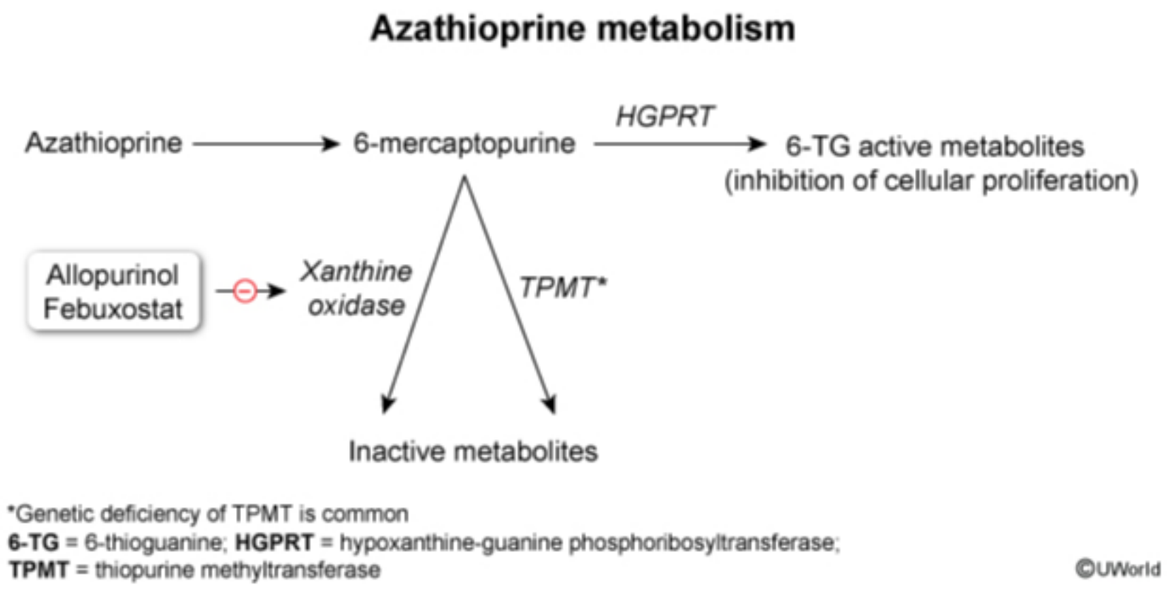

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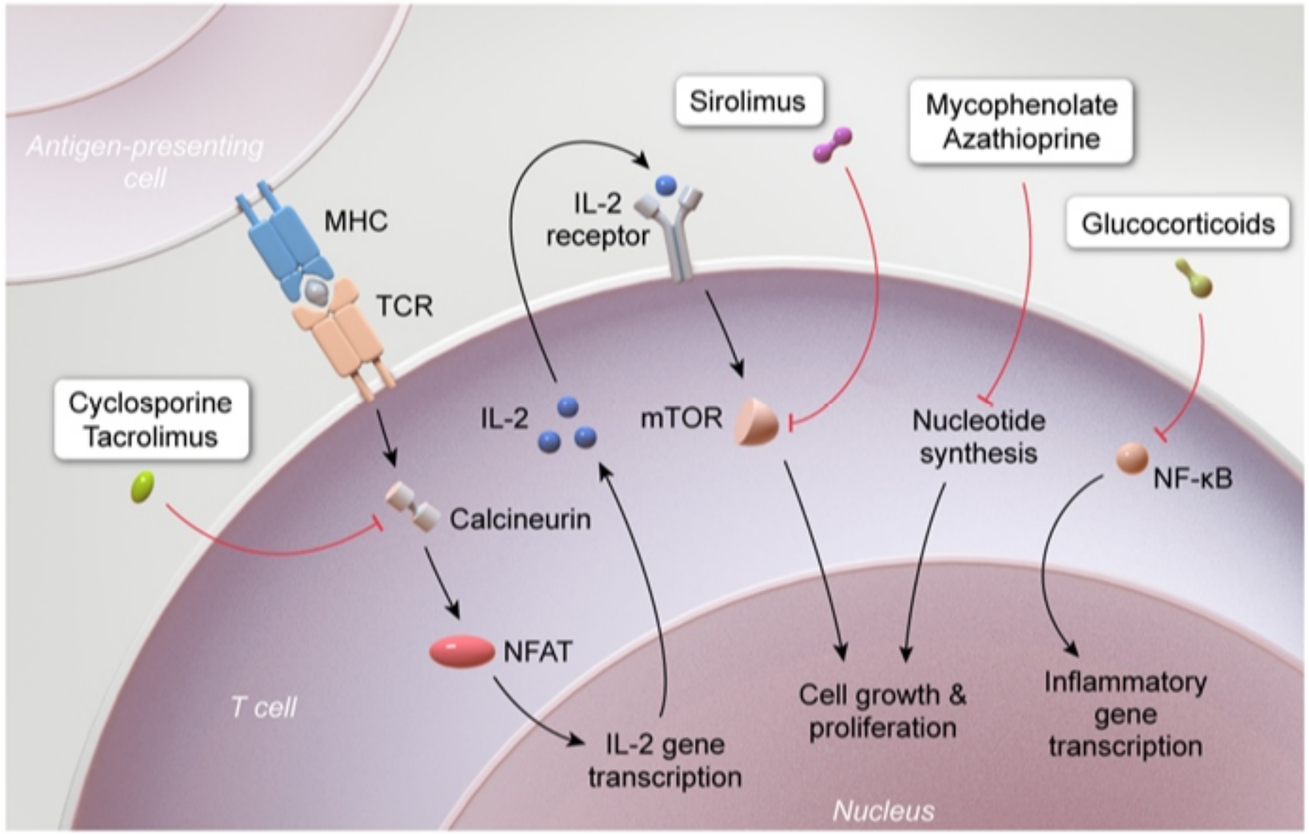
Mechanism of action of common immunosuppressants



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A 42-year-old woman is hospitalized due to fever and chills after a hemodialysis session. The patient has a history of end-stage kidney disease due to IgA nephropathy and recently began intermittent dialysis through a tunneled catheter. Medical history includes depression, for which she takes citalopram. Temperature is 38.4 C (101.1 F), blood pressure is 130/80 mm Hg, and pulse is 94/min. There is no erythema or tenderness at the catheter site, and the remainder of the physical examination shows no abnormalities. Blood cultures are obtained, and empiric vancomycin and ceftazidime are initiated. While receiving the intravenous vancomycin infusion, the patient reports a burning, itching sensation. Vital signs are unchanged, but repeat examination shows an erythematous rash involving the face and neck. She reports no history of drug allergy but has never received these antibiotics. Which of the following is the most likely underlying cause of this patient's current condition?

- A. Bacterial product release
- B. Cross-reacting antibodies
- C. Direct mast cell activation
- D. Drug-specific antibodies
- E. Serotonergic drug interaction

Submit

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- A. Bacterial product release (2%)
- B. Cross-reacting antibodies (5%)
- ✓ C. Direct mast cell activation (85%)
- D. Drug-specific antibodies (3%)
- E. Serotonergic drug interaction (3%)

Omitted
Correct answer
C

85%
Answered correctly

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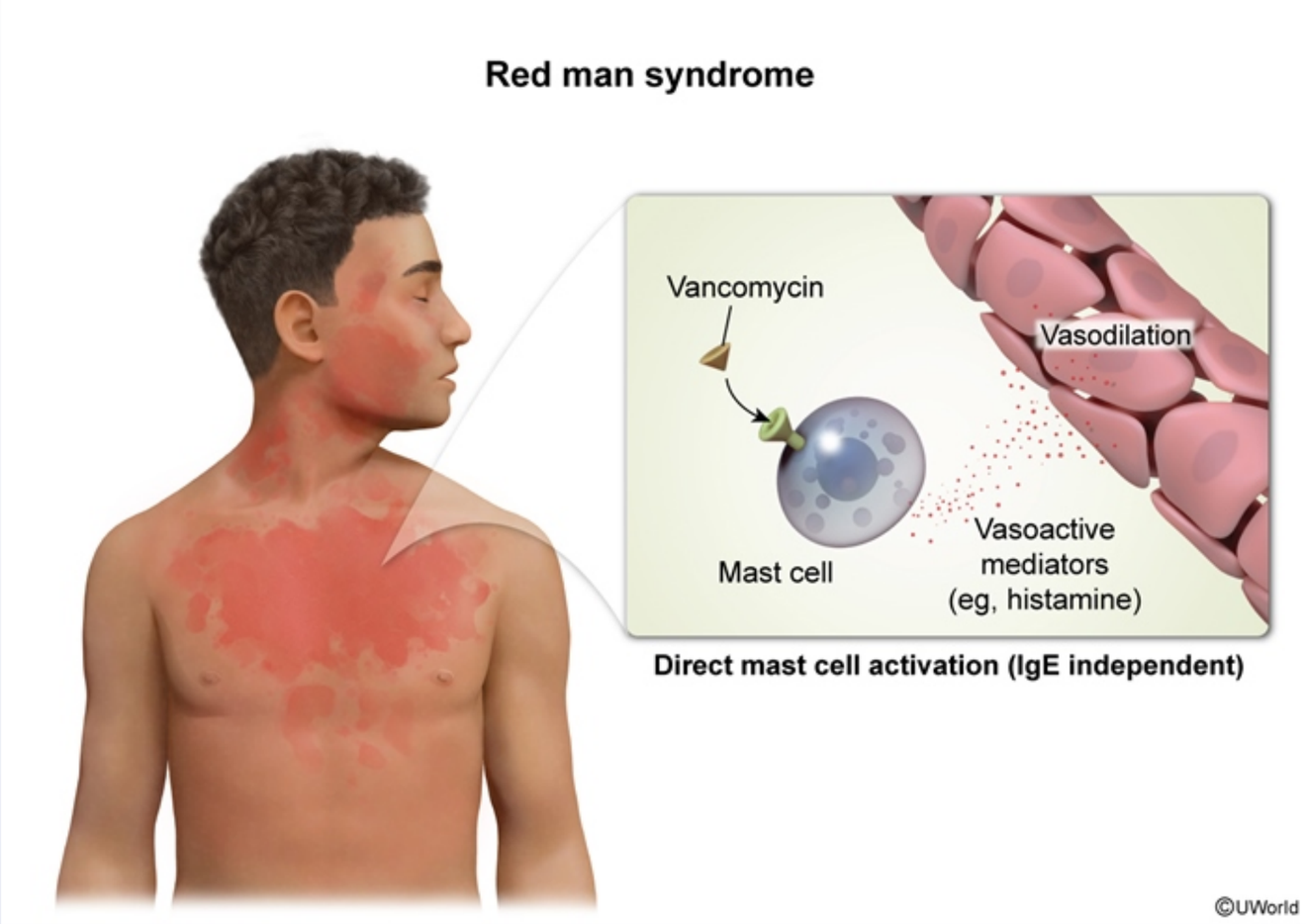
05/06/2020
Last Updated

Explanation

Red man syndrome



This patient was given vancomycin and shortly thereafter developed burning, itching, and an erythematous rash on the face and neck, raising strong suspicion for **red man syndrome** (RMS). RMS is a **nonallergic reaction** that occurs when vancomycin is infused too **rapidly**; rapid vancomycin infusion can **directly activate mast cells**, leading to the release of potent vasoactive mediators (eg, **histamine**).

Manifestations of RMS include flushing, pruritus, and an erythematous rash, which is usually seen on the upper torso, neck, and face. Myalgias and hypotension can occasionally occur. Discontinuation of the vancomycin and administration of diphenhydramine are usually curative. Because

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(Choice A) Patients with spirochetal illness (eg, syphilis, Lyme disease) can develop the Jarisch-Herxheimer reaction after the initiation of antimicrobial therapy. It is caused by massive release of bacterial products into the circulation due to widespread bacterial lysis. However, most cases arise several hours (not minutes) after antimicrobial therapy and are marked by high fever and worsened constitutional symptoms (eg, headache, myalgia).

(Choices B and D) Antibody-mediated drug reactions generally require previous exposure (sensitization) to the medication. This patient who has never received vancomycin is unlikely to have an antibody-mediated reaction; furthermore, such reactions are rare with vancomycin and are usually marked by urticaria, pruritus, hypotension, and angioedema.

(Choice E) Serotonergic drug interactions are most common with drugs that affect the serotonin system such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and certain antiemetics (eg, ondansetron). However, most cases are marked by alterations in autonomic function (eg, hypertension, tachycardia, hyperthermia), and rash is unusual.

Educational objective:
Red man syndrome (RMS) is the most common adverse reaction to vancomycin. It occurs due to rapid vancomycin infusion, which leads to the direct activation of mast cells and the subsequent release of vasoactive mediators. Patients develop flushing, pruritus, and an erythematous rash on the upper torso, face, and neck within minutes of initiation. Because RMS is not a true allergic reaction (not IgE mediated), vancomycin can be restarted at a slower rate of infusion once symptoms resolve.

Pharmacology	Allergy & Immunology	Drug allergy
Subject	System	Topic

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Pharmacology	Allergy & Immunology	Drug allergy
Subject	System	Topic

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